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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,942	02/18/2000	Jean-Marc Balloul	032751-027	9626

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EXAMINER	
FOLEY, SHANON A	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 11/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/506,942	BALLOUL ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44,46,48,49,55,56,62,64,65,69,71-75,79 and 80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,46,48,49,55,56,62,64,65,69,71-75,79 and 80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/043,933.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 16, 2005 has been entered.

Claims 44, 46, 48, 49,55, 56, 62, 64, 65, 69, 71-75, 79 and 80 are pending and under consideration.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 44, 46, 48, 55, 56, 62 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al. (Lancet. June, 1996; 374: 1523-1527), Galloway (Infectious Agents and Disease. 1994) 3: 187-193), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), Boursnell et al. (US 5,719,054), Bubenik et al. (International Journal of Oncology. 1996; 8: 447-481), Bash et al. (Journal of Immunotherapy. 1993; 14: 269-272) and Sutter et al. (US 6,440,422).

Applicant argues that the therapeutic strategy of Bubenik et al. is deficient because it requires separate and repeated injections of IL-2 and does not suggest expressing IL-2 from a vector. Applicant further argues that there is no reasonable expectation of success for achieving the adjuvanting effect observed from repeated injections from an MVA vector expressing IL-2 with four papillomavirus proteins.

Applicant's arguments have been fully considered, but are found unpersuasive. The teachings of Bubenik et al. provide a clear, prima facie obvious motivation to include IL-2 in a papillomavirus therapy with a reasonable expectation of success because IL-2 augments the immune response to papillomavirus polypeptides and increases protective efficacy, see page 478, Figure 1 on page 479 and the discussion section.

It is also maintained that it would have been prima facie obvious to one of ordinary skill to co-express IL-2 with the E6 and E7 therapeutic papillomavirus polypeptides of Galloway, Lowy, Boursnell and Borysiewicz, and the protective papillomavirus L1 and L2 polypeptides of Galloway, Lowy and Hagensee, from the MVA expression vector of Meyer et al. to avoid multiple injections of IL-2. This last motivation was recognized by applicant on page 17 of the response filed October 7, 2004, in which applicant states that the multiple injections with IL-2 of Bubenik et al. "would be very difficult to implement in human patients".

Nonetheless, the teachings of Bash et al. are now applied as evidence to support the Office's position (gleaned from the prior art previously cited) that expression of IL-2 from a vaccinia vector is produced in sufficient amounts to augment an immune response against tumors. Bash et al. teach therapeutic efficacy in tumor immunotherapy by administering a vaccinia vector expressing IL-2. The vaccinia-IL-2 vector of Bash et al. not only augments the

immune response, but also abolishes tumorigenicity in tumor cells and *in vivo*, delays the onset of tumorigenesis and shows regression of existing tumors, see the entire reference. Therefore, the teachings of Bash et al. clearly demonstrate a reasonable expectation of success for maintaining the augmentation of the immune response against papillomavirus polypeptides, observed by Bubenik et al., when expressed from a vaccinia expression vector.

Applicant also asserts that there is a lack of a reasonable expectation of success for simultaneous expression of multiple genes in a vaccinia vector. Applicant states that the art recognizes that expression of four gene sequences in a single vaccinia vector to be problematic and concludes that even more difficulty would be present when expressing a fifth gene.

Applicant is apparently referring to a previous argument presented in view of a discussion present in Boursnell in the paragraph bridging columns 9 and 10. As discussed previously (see page 4 of the Office action mailed December 28, 2004), applicant is misinterpreting the discussion by Boursnell in this paragraph. Boursnell is explaining that existence of extraneous marker sequences previously caused difficulty in expressing multiple genes from vaccinia vectors. Boursnell follows this explanation with a review of methods that were developed to allow elimination of these marker sequences, see column 10, lines 1-8. Boursnell also clearly demonstrates that any previous difficulties in expressing multiple sequences is eliminated by providing four HPV unfused genes in a vaccinia vector, see Figure 26c as well as column 3, lines 29-35 and column 8, lines 24-37. In any case, the instant claims, drawn to compositions "consisting of" certain elements, do not allow for the expression of any extraneous marker sequences. Furthermore and regardless of any obviated difficulties for using vaccinia discussed by Boursnell, the instant claims require MVA. MVA is highly attenuated and

is replete with genome deletions, which allow for multiple heterologous insertions, see the teachings of Meyer or Sutter.

Meyer et al. teach six major deletion sites, I, II, III, IV, V and VI, that are not essential to virus replication in the attenuated vaccinia virus, MVA. Meyer et al. do not teach heterologous expression of a gene from MVA. However, Sutter et al. explicitly claim an MVA vector expressing a five heterologous genes under the control of separate promoters, see claims 16 and 24.

One of ordinary skill in the art at the time the invention was made would have been motivated to express the four therapeutic and protective papillomavirus genes of Galloway, Lowy, Boursnell, Borysiewicz and Hagensee and the IL-2 of Bubenik and Bash in the MVA vaccinia vector of Meyer et al. and Sutter et al. because of its efficient heterologous gene expression and its extreme degree of attenuation, see column 2, line 30 to column 3, line 15 of Sutter et al. Therefore, it is maintained that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of expressing E6, E7, L1 and L2 papillomavirus polypeptides and IL-2 in the MVA vaccinia vector of Meyer et al. and Sutter et al. because Meyer et al. teach that MVA possesses multiple insertion sites for heterologous genes and Sutter et al. explicitly claim expressing five heterologous genes from five of the deletion sites of MVA, see claim 16. Therefore, in view of the teachings of Sutter et al., the ordinary artisan would have recognized that multiple expression of heterologous genes could have been successfully accomplished in an MVA vector.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536), Hagensee et al. (Journal of Virology. 1993; 67 (1): 315-322), Borysiewicz et al.

(Lancet. June, 1996; 347: 1523-1527), Galloway (Infectious Agents and Disease. 1994; 3: 187-193), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), Boursnell et al. (US 5,719,054), Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481), Bash et al. (Journal of Immunotherapy. 1993; 14: 269-272) and Sutter et al. (US 6,440,422) as applied to claims 44, 46, 48, 55, 56, 62 and 64 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105) for reasons of record.

Applicant reiterates the arguments presented for claim 48, from which claim 49 depend.

These arguments are found unpersuasive and the rejection is maintained for reasons of record. The rebuttal for these arguments is repeated herein.

Claims 65, 69, 71, 72, 74, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Meyer et al. (Journal of General Virology. 1991; 72: 1031-1038), Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481), Boursnell et al. (US 5,719,054), Bash et al. (Journal of Immunotherapy. 1993; 14: 269-272) and Sutter et al. (US 6,440,422).

Applicant argues that Borysiewicz does not suggest including IL-2 and does not teach independent expression of the HPV and immunostimulator gene sequences. Applicant reiterates that the repeated injection method of IL-2 of Bubenik is not equivalent to IL-2 expressed in an MVA vector with papillomavirus polypeptides.

Applicant's arguments have been fully considered, but are found unpersuasive. Bubenik clearly teaches augmenting an immune response to papillomavirus polypeptides and increasing protective efficacy by administering IL-2, see page 478, Figure 1 on page 479 and the discussion section of Bubenik et al. One of ordinary skill in the art would be motivated to avoid multiple

administrations of IL-2. Bash et al. teach sufficient amounts of IL-2 expressed from a vaccinia vector to augment an immune response against tumors. The vaccinia-IL-2 vector of Bash et al. not only augments the immune response, but also abolishes tumorigenicity in tumor cells and *in vivo*, delays the onset of tumorigenesis and shows regression of existing tumors, see the entire reference. Therefore, the teachings of Bash et al. clearly demonstrate a reasonable expectation of success for maintaining the augmentation of the immune response against papillomavirus polypeptides, observed by Bubenik et al., when expressed from a vaccinia expression vector.

Applicant also reiterates the difficulties discussed by Boursnell regarding multiple independent expression sites in vaccinia discussed by Boursnell.

The discussion of Boursnell regarding previous difficulties for expressing multiple genes in vaccinia is irrelevant since Boursnell follows the discussion with solutions to overcome the difficulties. Also, Boursnell also clearly demonstrates that any previous difficulties in expressing multiple sequences is eliminated by providing four HPV unfused genes in a vaccinia vector, see Figure 26c as well as column 3, lines 29-35 and column 8, lines 24-37. In addition, the instant composition requires the specific vaccinia vector, MVA. Both Meyer and Sutter describe the extent of genome that is deleted in MVA and Sutter specifically teach that five of the six deletion sites within the MVA vector is available for heterologous expression. Therefore, from the teachings of Meyer and more particularly Sutter, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of expressing multiple genes from separate independent control elements within MVA.

Claim 75 is rejected under 35 U.S.C. 103(a) as being unpatentable over Borysiewicz et al. (Lancet. June, 1996; 347: 1523-1527), Meyer et al. (Journal of General Virology. 1991; 72:

1031-1038), Bubenik et al. (International Journal of Oncology. 1996; 8: 477-481), Boursnell et al. (US 5,719,054), Bash et al. (Journal of Immunotherapy. 1993; 14: 269-272) and Sutter et al. (US 6,440,422), as applied to claims 65, 69, 71, 72, 74, 79 and 80 above, and further in view of Crook et al. (Cell. 1991; 67: 547-556) and Munger et al. (EMBO Journal. 1989; 8: 4099-4105),

Applicant cites the arguments presented for claims 65 above.

Applicant's arguments were fully considered, but were found unpersuasive. The rebuttal for these arguments is incorporated herein.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is 2-0898. The examiner can normally be reached on 6:00 AM - 2:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 2-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shanon A. Foley
Primary Examiner
Art Unit 1648